

In the claims:

Please amend the claims as follows:

1. (Thrice Amended) A [logically-ordered,] spatially-addressable array of at least [10] 500 different compounds, each of which is in solution, said compounds having a same common linear, branched or cyclic molecular core comprising at least three atoms of carbon, nitrogen, oxygen, phosphorus or sulfur and at least two structural diversity elements attached thereto, ~~[wherein the molecular cores have attachment points for the structural diversity elements, an ability to present the structural diversity elements in controlled varying arrangements, and an ability to be constructed in a rapid concerted fashion, said array comprising at least a first sub-array and a second sub-array, wherein the compounds composing the first sub-array each have at least one common structural diversity element, the compounds composing the second sub-array each have at least one common structural diversity element, and the first and second sub-arrays are different, and]~~ wherein the compounds [composing each sub-array] of the array differ from one another by at least one change in a structural diversity element.

Claims 2 and 3, lines 1-2 of each: change "molecular construct" to --compound--.

Claim 5 and 6, lines 1-2 of each: delete "molecular construct".

10. (Thrice Amended) A method of making a [logically-ordered,] spatially-addressable array of at least 500 different compounds, each of which is in solution, said compounds having a same common linear, branched, or cyclic molecular core comprising at least three atoms of carbon, nitrogen, oxygen, phosphorus or sulfur and at least two structural diversity elements attached thereto, ~~[wherein the~~

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~~molecular cores have attachment points for the structural diversity elements, an ability to present the structural diversity elements in controlled varying arrangements, and an ability to be constructed in a rapid concerted fashion,]~~ said array comprising at least a first sub-array and a second sub-array, wherein the compounds composing the first sub-array each have at least one common structural diversity element, and the compounds composing the second sub-array each have at least one common structural diversity element, said method comprising the steps of:

(a) providing [a plurality of] at least 500 reaction vessels organized into at least [the] first and second sub-arrays;

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(b) adding reactants to each of the reaction vessels in a manner such that, when reacted, the reactants form the compounds of the sub-arrays in the array, and such that the compounds composing each sub-array differ from one another by one change in a structural diversity element; and

(c) concurrently reacting the contents of [each] the reaction vessels under appropriate solution-phase conditions in one or more cycles to form [the] all compounds of the sub-arrays in the [logically-ordered] array.

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11. (Twice Amended) A method of making a spatially-addressable combinatorial array of at least 500 different compounds in solution in multiple cycles, said method comprising the steps of:

(a) apportioning into a plurality of reaction vessels that are identifiable by their spatial addresses (i) a first plurality of compounds, each compound in the first plurality of compounds comprising a same first reactive group and a different first structural diversity element such that the compounds composing the first plurality differ from one another, with one first compound per reaction vessel; and (ii) a second compound comprising a second reactive group and

a second structural diversity element, with one second compound per reaction vessel; [and]

(b) concurrently reacting said first and second compounds in each of the plurality of reaction vessels under solution phase conditions wherein each of the first and second reactive groups react with one another by an addition reaction to form a compound; and

(c) repeating steps (a) and (b), thus forming the combinatorial array of compounds in solution;

wherein each compound composing the combinatorial array comprises a same common linear, branched, or cyclic molecular core comprising at least three atoms of carbon, nitrogen, oxygen, phosphorus or sulfur having [and] the first and second structural diversity elements attached thereto, and further wherein the compounds composing the array differ from one another by at least one change in a structural diversity element [the molecular cores have attachment points for the structural diversity elements, an ability to present the structural diversity elements in controlled varying arrangements, and an ability to be constructed in a rapid concerted fashion].

12. (Twice Amended) The method of [claims 10 or] claim 11, further including, after step a) or step b), the step of formatting the contents of the reaction vessels into a spatially-addressable array.

Please cancel claims ~~8, 9, 14, and 15.~~

Please add the following new claims.

16. (New) The ~~combinatorial~~ array of claim 1, having at least 1000 ~~different~~ compounds.

17. (New) The method of claim 10, wherein the combinatorial array comprises at least 1000 compounds.

18. (New) The method of claim 11, wherein the combinatorial array comprises at least 1000 compounds.

19. (New) ~~The combinatorial array of claim 1, wherein the compounds of the array provide structure activity relationships useful in the selection of one or more optimum compounds.~~

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20. (New) The method of claim 10, wherein the compounds of the array provide structure activity relationships useful in the selection of one or more optimum compounds.

21. (New) The method of claim 11, wherein the compounds of the subarrays provide structure activity relationships useful in the selection of one or more optimum compounds.

22. (New) A method for making a spatially-addressable combinatorial array of compounds in solution, the compounds having a common molecular core structure and at least two structural diversity elements, wherein the array comprises at least 500 different compounds, the method comprising:

(a) selecting reagents suitable for preparing the compounds of the array;

(b) providing at least 500 spatially-addressable reaction vessels;

(c) apportioning the reagents into the reaction vessels; and

(d) concurrently reacting the reagents in the reaction vessels in one of more cycles under solution phase conditions such that all the compounds of the array are formed in solution;

wherein each compound composing the combinatorial array comprises a same common linear, branched, or cyclic

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molecular core comprising at least three atoms of carbon, nitrogen, oxygen, phosphorus or sulfur, said core having at least two structural diversity elements attached thereto, and further wherein the compounds composing the array differ from one another by one at least one change in a structural diversity element.

23. (New) The method of claim 22, further including, after step b) or step c), the step of formatting the contents of the reaction vessels into a spatially-addressable array.

24. (New) The method of claim 22 wherein the reagents in at least 80 reaction vessels are concurrently reacted per cycle.

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25. (New) The method of claim 22 wherein the compounds of the subarrays provide structure activity relationships useful in the selection of one or more optimum compounds.

#### REMARKS

The cross-reference to related applications in the specification has been amended to update the status of applicants' parent application. This change overcomes the informality noted at page 2, paragraph 4 of the office action.

The office action requested clarification for the use of the term "IND" on page 16 of the specification. In response, applicants confirm that the term "IND" is in fact used as a shorthand notation for "Investigational New Drug" as correctly surmised by the Examiner. The specification has been amended to insert a definition for this term. Also, a few errors of a typographical nature have been corrected. No new matter has been introduced in making these changes.

The office action notes that the prior art references submitted by the applicants could not be located in

the file of the parent application. Applicants do not understand this comment because the previous Examiner confirmed that he did have copies of these references and that he reviewed them. In addition, applicants note that copies of these references are currently available in the file of copending application 09/009,844 which is in group 1611 with Examiner P.K. Sripada. For the Examiner's convenience, copies of the references will be provided.

Page 2 of the office action indicates that the declaration is defective and that the petition to correct inventorship of this application is deficient because a listing of the entire inventive entity has not been submitted. Applicants respectfully request reconsideration of these objections.

In the present application as filed, there was submitted a declaration signed by five of the six listed inventors. This declaration, a copy of which is submitted herewith, clearly shows that there are six co-inventors for the subject matter disclosed and claimed in this application. Thus, applicants do not understand how a listing of the entire inventive entity has not been submitted.

As to the "missing" signature of Paul Furth, applicants have submitted copies of a petition under 37 CFR 1.48, along with the supporting documentation and a decision which granted this petition in the parent application. As the circumstances regarding the non-signing inventor have not changed in this continuation application, it is submitted that that petition controls and should be adopted in this application. Thus, applicants submit that there are no deficiencies in the inventors' declaration or in their grantable petition for proceeding in the absence of Paul Furth's signature.

Claims 1-7 and 10-13, as amended, and new claims 16-25 appear in this application for the Examiner's review and consideration. Claims 1, 10, 11 and 12 have been amended to more particularly point out and distinctly claim the subject

matter which Applicants regard as their invention. Claims 16-25 have been added. The claim amendments and cancellations have been made to expedite prosecution of the present application. Support for these amendments can be found throughout the specification, e.g., at page 10, lines 3-7; page 12, lines 17-19; page 14, lines 23-24 and the example on pages 27-29. As no new matter has been added, these claim changes and additions should be entered at this time.

Claims 8-9, 14 and 15 have been canceled without prejudice or disclaimer of the subject matter of those claims; Applicants reserve the right to present these claims, or other claims directed to disclosed subject matter, in this or another application. Thus, all rejections of these claims have been rendered moot.

Rejection of claims under 35 USC 112, first paragraph

In the Office Action, claims 1-15 were rejected under 35 USC 112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Applicants disagree and respectfully submit that this rejection does not apply to the claims as amended.

Page 3 of the Office Action states that the "specification disclosure does not have sufficient guidance to which core compounds and which structural diversity elements are used to make the instant array." This rejection is respectfully traversed.

The pending claims are directed to arrays of compounds and to methods for making the arrays. As stated in the specification (e.g., at page 15, lines 2-7), the compounds of the arrays can be tested for use in a variety of applications. As the Examiner will appreciate, different compounds may have different applications; accordingly, different cores may be selected readily by one of ordinary

skill in the art depending upon the particular uses contemplated.

As further stated in the specification (e.g., at page 18, lines 23-30), a variety of molecular cores can be used; these cores can be selected according to the particular application desired. The specification provides explicit guidance as to the criteria for selecting a core, including, *inter alia*, the ability of the core to a) present attachment points for structural diversity elements; b) present the structural diversity elements in controlled, varying spatial arrangements; and c) be constructed concurrently in a rapid concerted fashion. One of ordinary skill in the art would readily be able to select suitable molecular cores, given the guidance provided by the specification, using no more than their knowledge in the field and optionally with routine experimentation.

Moreover, the specification provides (e.g., at page 19, line 1 to page 21, line 2) extensive non-limiting examples of molecular cores which can be used in the arrays and methods of the invention as claimed. Furthermore, the specification provides examples of reactions which can be used to prepare the molecular cores of the compounds of the invention, including well-known reactions such as Diels-Alder reactions, Ugi and Passerini reactions, Simmons-Smith cyclopropanations, Darzens glycidic ester condensations, and rhodium-catalyzed carbene additions (see, e.g., p. 21, lines 3-9). In addition, one of ordinary skill in the art of chemistry is well aware of numerous other reactions that would operate in an equivalent manner to those that are specifically enumerate therein. In light of this guidance, one of ordinary skill in the art would have absolutely no problem in selecting an appropriate molecular core that would meet the criteria set forth in the specification.

The Office Action further states that the specification "does not disclose any screening assays in which compounds of the invention are screened. The specification



fails to give adequate guidance in selecting an assay in which the compounds of the array are screened . . . ." While Applicants do not agree with this statement, claims 14-15 (the only previously-pending claims to require screening) have been cancelled to expedite prosecution of the present application. As none of the presently-pending claims requires screening of the compounds, the Examiner's statement is not applicable.

For at least the above reasons, reconsideration and withdrawal of the rejection under 35 USC 112, first paragraph, is proper and the same is requested.

Rejection of claims under 35 USC 101 and 112, first paragraph

Claims 1-9 were rejected under 35 USC 101, with the Office Action stating that "the claimed invention is not supported by either a specific asserted utility or a well established utility." This rejection is respectfully traversed.

Current claims 1-7, as amended, and new claims 16 are directed to combinatorial arrays of compounds in which the arrays have at least 500 different compounds. Combinatorial arrays of compounds are useful for identifying compounds having a desired property. For example, at page 16, lines 3-10, the present specification states:

An application of this invention is the rapid determination and optimization of desired biological or physical activity. An array is screened and the optimum candidate is chosen. This process can be continued in n dimensions to provide an absolute structure activity relationship ("SAR") picture of the candidate and selection is speeded by the rapid modular synthesis of arrays for use in testing."

It will be appreciated that, in the case of screening applications, the particular assay used to screen the libraries can be selected according to the desired application. A wide variety of assays are available from commercial sources (e.g., in the form of kits) and/or have

been described in the scientific literature. In addition, the arrays can be used to provide structure activity relationships which are useful in selecting one or more optimum compounds for a particular use. This feature of the invention is presented in claims 19 to 21. Thus, skilled artisans could routinely select an appropriate assay for a particular application using their knowledge and, if necessary, no more than routine experimentation. This demonstrates that one of ordinary skill in the art would appreciate that the claimed arrays are useful, e.g., in determination or characterization of physical or biological activity of compounds.

Page 5 of the Office Action states that "the specification does not assert any specific utility . . . . In the absence of any data, these libraries are deemed to be not supported by a specific asserted utility." Applicants respectfully disagree.

As stated above, the libraries of the invention are useful for a wide variety of applications. The use of combinatorial libraries in drug discovery and other applications is well known and well established. For example, in a review article by Gordon et al. (Gordon, E.M., Barrett, R.W., Dower, W.J., Fodor, S.P.A., & Gallop, M.A. (1994) "Applications of combinatorial technologies to drug discovery. 2. Combinatorial organic synthesis, library screening strategies, and future directions." *J. Med. Chem.*, 37, 1385-1401 (hereinafter the "Gordon paper") previously cited to the Examiner), the preparation and use of combinatorial libraries for drug discovery was discussed. While the instant libraries differ from the libraries described in the Gordon paper (that paper was largely concerned with libraries of compounds attached to a solid support), the utility of combinatorial libraries in general has long been known and described. The use of the libraries of the invention, e.g., in screening and to facilitate simultaneous testing of multiple compounds, has been clearly asserted and is well established. In addition, the arrays can be used to provide structure activity

relationships which are useful in selecting one or more optimum compounds for a particular use.

Claims 1-9 were additionally rejected under 35 USC 112, first paragraph because "one skilled in the art clearly would not know how to use the claimed invention." This rejection is also traversed.

As described above, the claimed arrays are useful, e.g., for determination and/or optimization of biological or physical activity. Skilled artisans would be able, e.g., to select an appropriate assay for a particular testing or screening application using no more than routine experimentation. Thus, contrary to the assertion in the Office Action, one skilled in the art would know how to use the claimed invention, and could use the invention using no more than routine experimentation.

Page 6 of the Office Action states that "the claims encompass any number and/or type of compounds." Applicants respectfully point out that amended claim 1 requires that the claimed array include at least 500 different compounds, and that the compounds include a common molecular core and at least two structural diversity elements. As previously discussed, the specification provides examples of, and considerable guidance in the selection of, molecular cores and diversity elements. Moreover, the specification describes (in the Example) the synthesis of an array having over 10,000 spatial addresses for synthesis of compounds. The teachings of the specification fully enable the present claims and that only routine experimentation would be needed to make and use these arrays.

For at least the above reasons, reconsideration and withdrawal of the rejections under 35 USC 101 and 35 USC 112, first paragraph, is proper and the same is requested.

Rejection of claims under 35 USC 112, second paragraph

Claims 1-15 were rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly

point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants submit that this rejection does not apply to the pending claims.

Claims 1, 8, 10 and 11 were rejected as being vague and indefinite by reciting the phrase "'logically-ordered', 'spatially-addressable array of compounds'." While Applicants do not agree that the term "logically-ordered" is vague and indefinite, this term has been cancelled. In addition, the phrase "spatially-addressable" is not vague and indefinite. A spatially-addressable array is an array in which individual addresses (i.e., reaction vessels) are separated in space and can be accessed or addressed individually. See, for example, the specification at pages 27-29 (the Example); Figures 1 and 2; and page 46, Table 4. One of ordinary skill in the art would have no problem in understanding the phrase "spatially-addressable array" in light of the teachings of the present specification.

The phrases "an ability to present the structural diversity elements in controlled varying arrangements" and "an ability to be constructed in a rapid concerted fashion" were also objected to in the Office Action. While Applicants do not concede the unacceptability of these terms, the present claims have been amended to omit this language.

Claim 10 was rejected for reciting "the first and second sub-arrays are different." Claim 10, as presently pending, now does not include this language. Thus, this rejection does not apply.

Claim 10 was also rejected as being vague and indefinite by reciting "a) providing a plurality of reaction vessels organized into the first and [sic, second] sub-array . . .". This rejection is traversed. Claim 10, as amended, recites: "(a) providing at least 500 reaction vessels organized into at least first and second sub-arrays". As stated in the specification, e.g., at page 9, lines 32-35, a sub-array is a set of spatial addresses within a given array; in other words, a sub-array is a subset of an array. Although

vessels (or addresses or compounds) are spatially separated from one another, they can nevertheless be grouped together in an array, and an array can include two or more subarrays. As recited in amended claim 10, reactants are added to each of the reaction vessels such that the compounds composing each sub-array differ from one another by at least one change in a structural diversity element. To achieve this result, different reagents are added to different reaction vessels, as described throughout the specification (see, e.g., page 15, lines 13-22; the Examples; and Tables 1- 4), and the contents of the reaction vessels are concurrently reacted in at least one and preferably multiple cycles (see, e.g., the Example). Applicants submit that one of ordinary skill in the art would understand this claim language and that the amended claim is not vague or indefinite.

The Office action also states that "[c]laim 11 is vague and indefinite by reciting 'apportioning into reaction vessels identifiable by their spatial addresses'". Applicants do not agree. As the specification makes clear, a spatial address refers to the position of a vessel or compound in an array. One of ordinary skill in the art would immediately realize that the reactants can be apportioned into these vessels in order to form the compounds. Accordingly, this language cannot be vague or indefinite.

Claim 11 was rejected as being vague and indefinite by reciting ". . . the first plurality of [sic] comprising a same first . . .". Claim 11 has been amended to recite "each compound in the first plurality of *compounds* comprising a same first reactive group . . ."; that is, that each member of the first plurality of compounds includes the same first reactive group (e.g., an amine, an aldehyde, etc.). Applicants respectfully submit that this language is clear and is not vague or indefinite.

The Office Action also requested clarification of claim 11 in step b); in response, the claim has been amended to clarify that it is the first and second compounds in each

reaction vessel that are reacted. Applicants urge that this language is clear and is not indefinite.

Claim 12 was rejected as being vague and indefinite for reciting ". . . formatting the contents of the reaction vessels into a spatially-addressable array." In response, claim 12 has been amended to provide that the further formatting step can occur after step a) or step b). Applicants respectfully submit that this language is clear and unambiguous. Furthermore, the present specification, e.g., at page 28, lines 14 - 34, describes one example of formatting of an array according to the amended claims. Accordingly, Applicants urge that the amended claims are not vague and ambiguous, and that all rejections under 35 USC 112, second paragraph, are proper and should be withdrawn.

Accordingly, the entire application is now believed to be in condition for allowance, early notice of which would be appreciated due to the presence of the disclaimer.

No fee is believed to be due for the claim changes of this response. Should any fees be required, please charge them to Pennie & Edmonds llp deposit account no. 16-1150.

Respectfully submitted,

Date

10/4/99

  
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